Remarks

Claims 1, 5, 19, 21-27, 30, and 32-39 are pending in this application. All of the pending claims have been amended to more distinctly claim the present invention. Support for the amendments to the claims may be found in the originally filed claims and on page 16, lines 13-22. Applicants have also amended the Specification to include the subject matter of originally filed claim 5. None of the amendments add new matter.

Applicants respectfully submit that the pending claims are allowable for at least the following reasons.

A. The Pending Claims are Definite

In the instant Office Action, claims 1, 5, 19-27 and 30-39 are rejected as allegedly being indefinite for the reasons set forth on pages 3-7 of the Action. Although Applicants disagree, the claims are amended to expedite the prosecution of this application. In light of the claim amendments, Applicants respectfully submit that the rejections are moot.

For example, the rejections set forth in items 2.a) and b) on page 3 of the Office Action are obviated because pending claims 1 and 5 do not recite "acylhydroxamic acid" or "derivative." The rejections set forth in items 2.c)-h) are also obviated by the correction of the typographical/clerical errors in claims 1 and 5. For example, the typographical error noted in item 2.c) "imidazolylmethlyl" has been corrected in claim 1.

In addition, the rejections set forth in items 2.i-l) are obviated by the amendments to the Specification, whereby the subject matter of originally filed claim 5 is introduced into the Specification. The rejections set forth in items 2.m) and 2.p) are now moot because claims 20 and 31 are cancelled. Finally, Applicants have overcome the rejection set forth in item 2.o) by amending claim 24 to recite "chronic obstructive pulmonary disease" instead of reciting the acronym "COPD." Reconsideration and withdrawal of all of the rejections under 35 U.S.C. § 112, second paragraph are respectfully requested.

B. The Rejection Under 35 U.S.C. § 112, ¶¶1 and 2 Should Be Withdrawn

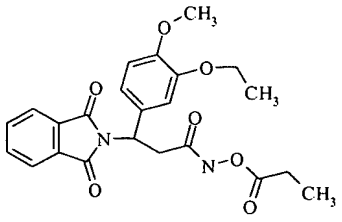
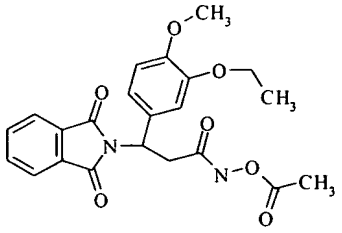
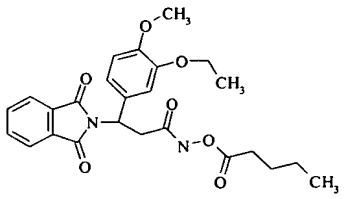
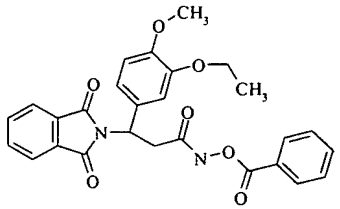
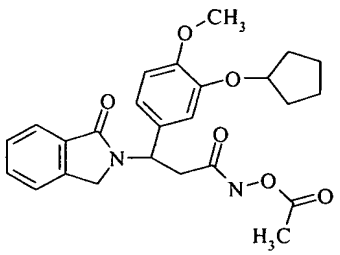
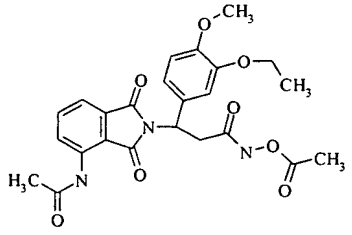
Claims 25, 26, 36, and 37 are rejected under 35 U.S.C. § 112, ¶1 as allegedly lacking enablement. Also, claims 19-27 and 30-33 are rejected under 35 U.S.C. § 112, ¶2 as allegedly being indefinite. In particular, it is alleged that the specification does not enable any person skilled in the art to use the invention commensurate in scope with claims 25, 26, 36, and 37. Office Action, page 2. Further, the Examiner alleges that determining whether a given disease responds or does not respond to the claimed compounds would require undue experimentation. *Id.* at page 5. Applicants respectfully disagree.

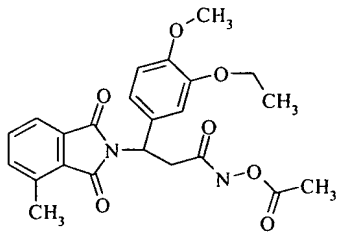
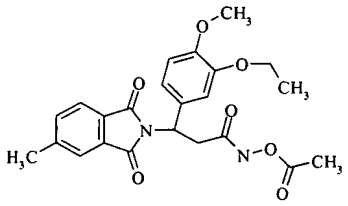
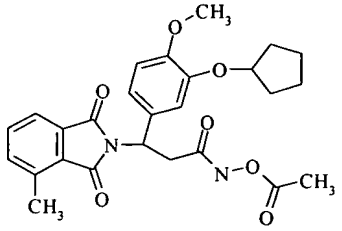
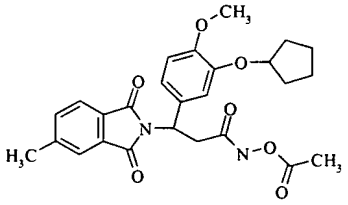
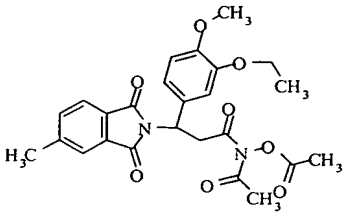
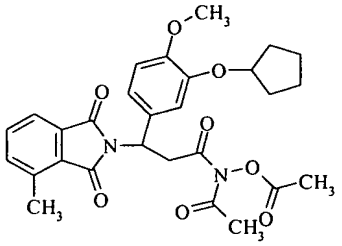
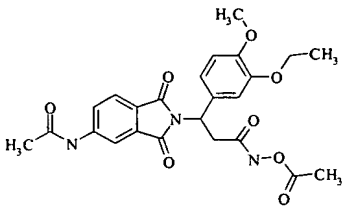
Without being bound by a particular theory, the literature references cited throughout the specification suggest that there is a strong correlation between elevated levels of serum TNFα levels in a subject and the occurrence or the progression of various diseases such as cancer, bone resorption diseases, cerebral malaria, reperfusion injury, and HIV infection. *See* specification, page 1, line 10 to page 12, line 3.

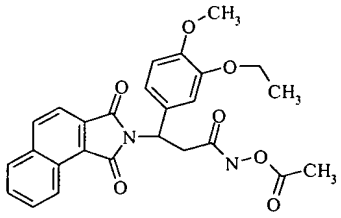
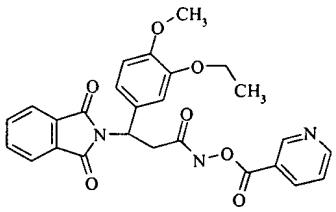
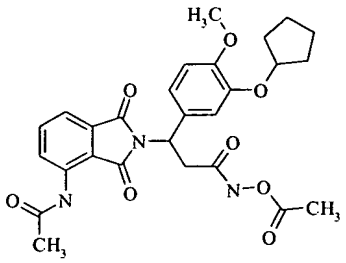
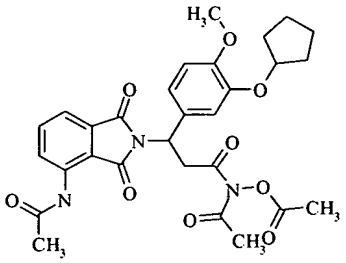
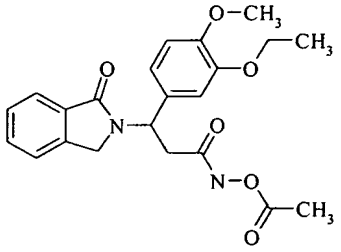
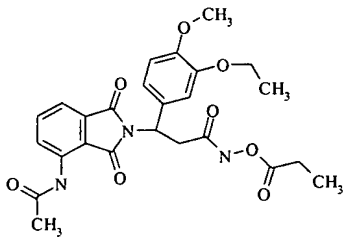
Without being bound by a particular theory, the literature references cited in the specification also suggest that there are several ways to reduce the serum levels of TNFα, thereby effectively treating such diseases. One way to reduce serum TNFα levels in a subject is by elevating levels of adenosine 3',5'-cyclic monophosphate (c-AMP) via the inhibition of cyclic nucleotide phosphodiesterases (PDE). *See*, specification, page 6, lines 14-20. Another way of reducing the serum levels of TNFα is via the inhibition of matrix metalloproteinases (MMP). *See*, specification, page 11, line 11 to page 12, line 3.

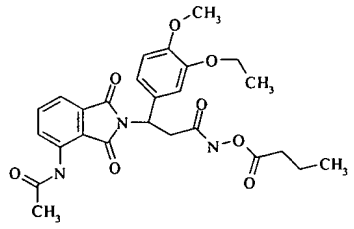
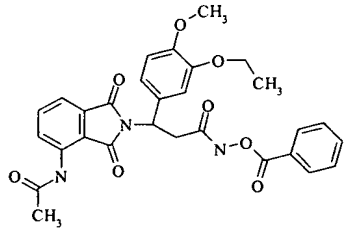
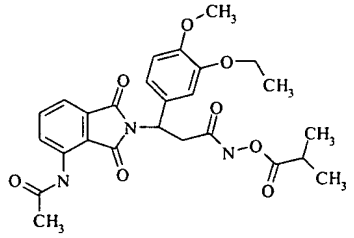
The compounds of the formula I, which are contained in the presently claimed compositions, have been shown *in vitro* to decrease the levels of TNFα. *See*, specification, page 12, lines 7-10. Furthermore, Applicants submit herewith IC_{50} values of several exemplary compounds of the invention. *See* Table 1, below. As shown in Table 1, exemplary compounds of the invention exhibit IC_{50} values in the nanomolar range. Therefore, it is evidenced that the claimed compositions can be effective in the treatment of a variety of diseases that are characterized by increased levels of TNFα, including cancer.

Table 1

Example	Structure	TNF IC_{50} (μM)
1		0.114
2		0.105
3		0.0919
4		0.48
5		0.26
6		0.02419

Example	Structure	TNF IC_{50} (μM)
7		0.03912
8		0.1001
9		0.07237
10		0.1605
11		0.1503
12		0.1049
13		0.1536

Example	Structure	TNF IC_{50} (μM)
14		0.671
15		0.723
16		0.0576
17		0.0725
18		0.396
25		0.0156

Example	Structure	TNF IC_{50} (μM)
26		0.01955
27		0.1524
28		0.04246

Applicants further submit that, contrary to the Examiner's position, the Specification is enabling and it would not require undue experimentation to determine whether a given disease responds or does not respond to the claimed compounds.

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent, coupled with information known in the art, without undue experimentation. *U.S. v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed. Cir. 1988) (emphasis added). The examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *Manual of Patent Examining Procedure* ("MPEP") § 2164.04 (citing *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993)). Accordingly:

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must be taken as being in compliance with the enablement requirement* ... unless there is *a reason to doubt the objective truth of the statements* contained therein which must be relied on for enabling support

* * *

> It is incumbent upon the Patent Office, whenever a rejection on this basis is made, to *explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning* which is inconsistent with the contested statement.

Id. (emphases added).

Applicants respectfully submit that the pending claims are enabled because the specification "contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented." *Id.* For example, the Specification teaches the skilled artisan how to make the compounds used in the claimed pharmaceutical compositions on pages 29-40 and 46-48. Further, the Specification teaches that these compounds are useful in treating cancer and other diseases on, *e.g.*, page 12, lines 11-19. Thus, all that is required by those of ordinary skill in the art is to take the described compounds and make pharmaceutical compositions using the compounds, the methods for which are described in the Specification at pages 41-45.

Furthermore, Applicants point out that the IC_{50} data provided herein certainly show that the claimed compositions are enabled. Despite this fact, the Examiner, based her own criteria set forth on pages 4-7 of the Office Action, alleges that the claims are not enabled. The Examiner appears to suggest that the instant Specification is not enabling unless Applicants demonstrate clinical efficacy of the claimed compositions akin to clinical efficacy that would be necessary to gain approval from the Food and Drug Administration. But, the Examiner seems to be confusing the requirements under the law for obtaining a patent with the requirements for obtaining governmental approval to market a particular drug for human consumption. *See, In re Brana*, 51 F.3d 1560, 1567 (Fed. Cir. 1993)).

To the extent that the data provided herein are *in vitro*, Applicants point out that to demonstrate utility, Applicants need only show that any given compound is pharmacologically active *in vitro*. *See, Cross v. Iizuka*, 753 F.2d 1040, 1051 (Fed. Cir. 1985) ("Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility.) (citations omitted). Further, "[i]f a statement of utility in the specification contains ... a connotation of how to use, and/or the art recognizes that standard modes of administration are

known and contemplated," the enablement requirement is satisfied. *Manual of Patent Examination and Procedure* § 2164.01(c) (citing, *inter alia*, *In re Brana*, 51 F.3d 1560, 1566 (Fed. Cir. 1993)). Therefore, it is clear that a sufficient guidance is provided in the specification so as to allow those of ordinary skill in the art to make and use the claimed invention.

The Examiner further alleges that the Specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with claims 25, 26, 36, and 37. But, the Examiner has not explained why she doubts the truth or accuracy of any statement in the supporting disclosure or presented any acceptable evidence or reasoning to back up her assertions. Instead, the Examiner has concluded, based solely on her reading of *In re Buting*, that "[t]he intractability of these disorders [*i.e.*, cancer] is clear evidence that the skill level in this art is low relative to the difficulty of the task." Office Action at page 2.

Applicants note that in *In re Buting* appellant was relying on evidence of efficacy against a spectrum of leukemia and ascitic and solid tumors in experimental mice of <u>two</u> of the claimed sulfones, as proof of the asserted utility. *In re Buting*, 418 F.2d 540, 540 (Cust. & Pat.App. 1969). As an initial matter, the Examiner is citing a case which was decided in 1969. Since then, even the Patent and Trademark Office Board of Patent Appeals and Interferences has recognized that substantial progress has been made in the study and treatment of cancer in the intervening years. *Ex Parte Chwang*, 231 U.S.P.Q. 751, 751 (P.T.O. Bd.Pat.App. & Int. 1986). Applicants also point out that the bis (beta-aziridino-ethyl) sulfones discussed in *Buting* are significantly different compounds, when compared to the acylhydroxamic acid derivatives that are contained in the claimed compositions. Finally, Applicants have presented IC_{50} values for 25 compounds that are disclosed in the instant Specification. Thus, while the Court of Customs and Patent Appeals may have decided that evidence of efficacy based on testing data for only two compounds was not sufficient to support the purported utility of Buting's bis (beta-aziridino-ethyl) sulfones, it does not follow that the same is true for the claimed compositions. Applicants respectfully submit, therefore, that the Examiner has not met her burden by providing a relevant factual basis for her allegation that the claimed compositions would not be generally effective in the treatment of cancer and other diseases recited in the instant claims.

Applicants also disagree with the allegation that determining whether a given disease responds or does not respond to the claimed compounds would require undue

experimentation. The standard that she has applied is legally incorrect: there is no requirement that those of ordinary skill in the art must be able to determine whether a given disease responds or does not respond to the claimed compounds. Instead, the standard is whether those of ordinary skill in the art would be able to make and use the claimed invention. *See Telectronics, Inc.*, 857 F.2d at 785. Thus, the Examiner's misapplication of the legal standard is at least an additional reason exists for withdrawing the rejection under 35 U.S.C. § 112.

In this regard, the Examiner is reminded that some factors that may --but need not[1]-- be considered in determining whether experimentation is undue include the quantity of experimentation necessary and the amount of direction or guidance provided. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). In *Wands*, the Court of Appeals for the Federal Circuit held that claims directed to immunoassay methods were enabled even though in order to practice the claimed invention, one would have to screen "hybridomas to determine which ones secrete antibody with desired characteristics." This was because "[p]ractitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody." *Id.* at 740.

As in *Wands*, the Examiner here is objecting to what is basically a screening step. Yet here, the screening is not nearly as complex, as the claimed invention is directed to the use of readily obtainable compounds, for which routes of administration and amounts are set forth in the specification in Examples 19-24, on pages 41-46. The skilled artisan can readily determine the IC_{50} for any given compound by using the methods described in the Specification at pages 26 and 27. The IC_{50} value that he/she determines is a good indication of which compounds will be useful in the treatment of the various diseases, including cancer. Moreover, the determination by a physician as to whether the claimed compositions are effective in treating, *inter alia,* cancer, in a given patient is a type of determination that is always made by physicians for every pharmaceutical. Indeed, the determination is a routine one that every physician is prepared to make, and which requires little or no effort. Therefore, Applicants respectfully submit that one reasonably skilled in the art could make or use the invention as claimed without undue experimentation.

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[1] *Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd.*, 927 F.2d 1200, 1230 (Fed. Cir. 1991), *cert. denied*, 502 U.S. 856 (1991) ("it is not necessary that a court review all the *Wands* factors to find a disclosure enabling. They are illustrative, not mandatory.").

In sum, Applicants respectfully submit that: (1) the specification provides sufficient information and guidance to those of ordinary skill in the art to make and use the claimed invention; and (2) to the extent any experimentation is necessary, such experimentation is not undue. Therefore, Applicants respectfully request that the rejection of the claims under 35 U.S.C. § 112, ¶¶ 1 and 2, be withdrawn.

C. The Double Patenting Rejection Should Be Withdrawn

On page 7 of the Office Action, claims 1 and 2 stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of U.S. Patent No. 6,699,899 ("the '899 patent"). Applicants point out that the pending claims are directed to pharmaceutical compositions comprising acylhydroxamic acid compounds and to methods of using said pharmaceutical compositions to treat a variety of diseases. In contrast, the claims of the '899 patent are directed to acylhydroxamic acid compounds *per se*. Consequently, the pending claims are patentably distinct from the claims of the '899 patent. Reconsideration and withdrawal of this rejection are respectfully requested.

Conclusion

In view of the foregoing, Applicants respectfully submit that all of the pending claims are allowable, and thus request the rejection of the claims be withdrawn.

Save for the fee that accompanies the Petition for Extension of Time, no fee is believed due for the submission of this paper. If an fees are required for the submission of this paper, or to avoid abandonment of this application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

Date: Sept. 2, 2005

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